

ABSTRACT FORM - The 1988 International Symposium on Pain Control and Medical Education

Clinical Pharmacology of Controlled-Release Codeine in Normal Subjects

R. Kalko*, G. Thomas, B. Grandy, N. Healy, J. Horodniak, B. Oshlack, and P. Goldenhelm

The Purdue Frederick Company, Norwalk, CT, USA

Codeine, often used for the treatment of mild to moderate pain, was formulated as a controlled-release tablet (CRC, 100, 150, and 200 mg). Five bioavailability studies were conducted as randomized, crossover designs in young, healthy male subjects. The area under the plasma codeine-concentration-time curve (AUC, ng/ml x hr), the maximal plasma codeine concentration (C_{max} , ng/ml), the time of maximal plasma codeine concentration (T_{max} , hr), and adverse experiences were assessed in each study. Both AUC and C_{max} data are normalized to a common dose of 100 mg codeine base irrespective of dose. 1. CRC was compared to a codeine sulfate tablet, in a single-dose study, in 20 subjects. The mean (se) AUC for CRC and the codeine sulfate tablet, respectively, was 1069 (66) and 969 (64). Similarly, mean C_{max} values were 137 (7) and 259 (21). Mean T_{max} was 3.3 (0.2) and 1.2 (0.1). Three side effects were reported with the 100 mg CRC tablet in comparison to six reports with the 60 mg codeine sulfate tablet. 2. In a single dose study, CRC was compared to codeine phosphate liquid in 13 subjects. AUC for CRC and the codeine sulfate liquid, respectively, was 1171 (66), and 1225 (66). Similarly, C_{max} was 146 (12) and 297 (12). T_{max} was 3.3 (0.2) and 1.2 (0.2). Five side effects were reported with the 100 mg CRC tablet and also with the 60 mg codeine phosphate solution. 3. The 100 mg CRC tablet was administered under fed (high fat meal) and fasted conditions in a single-dose comparative study in 23 subjects. AUC under fed and fasted conditions, respectively, was 1036 (64) and 903 (48). Similarly, C_{max} was 151 (10) and 137 (8). T_{max} was 4.5 (0.4) and 3 (0.3). Eleven side effects were reported under both fed and fasted conditions. 4. CRC, at doses of 100, 150, and 200 mg, was compared to 100 mg conventional oral codeine solution in 21 subjects, in a single-dose bioequivalence study. AUC for the treatments as listed above was 1012 (53), 992 (57), 1034 (50) and 1141 (48). C_{max} was 143 (7), 135 (9), 143 (10), and 235 (13). T_{max} was 3.3 (0.2), 3.4 (0.2), 3.2 (0.2), and 1.3 (0.1). The occurrence of side effects was 4, 20, 20, and 30. 5. Q12h CRC was compared to q6h conventional oral codeine solution after dosing to steady-state conditions in 21 subjects over four days each. AUC for CRC and the standard was 1201 (54) and 1159 (70), respectively. C_{max} was 193 (6) and 162 (10). T_{max} was 3.3 (0.2) and 1.2 (0.1). Relative to codeine levels, plasma morphine levels following CRC were not different from those following conventional oral codeine. The three different dosage strengths of CRC are bioequivalent; while the extent of codeine absorption following CRC is comparable to that following conventional oral codeine, CRC is associated with a significantly attenuated and prolonged maximal plasma codeine concentration. There was no evidence of "dose-dumping." While the ingestion of a high fat meal extended T_{max} , it did not affect the extent of codeine absorption. Steady state is achieved within one to two days of q12h CRC dosing. The metabolism of codeine to morphine is not different after CRC than after conventional oral drug. The values for AUC, C_{max} and T_{max} are remarkably consistent from study to study. Therapeutic evaluation of CRC is now warranted.

Deposition Exhibit

Purdue et al. v. Endo et al.
Nos. 00 Civ. 8079 (SHS),
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)

DX 1124

TLS 7-10-02

Trial Exhibit

Purdue et al. v. Endo et al.
Nos. 00 Civ. 8079 (SHS),
01 Civ. 2109 (SHS); 01 Civ. 8177 (SHS)

DX 2706

CONFIDENTIAL INFORMATION
Purdue Frederick Company

P 486917

THE 1988 INTERNATIONAL SYMPOSIUM ON PAIN CONTROL AND MEDICAL EDUCATION.
7th - 9th OCTOBER 1988, EDINBURGH, SCOTLAND

Instructions for abstracts

Type within the large rectangle your entire abstract including title (underlined), name(s) of author(s), institution and address exactly as shown below, free of smudges and errors. Please practice first in a rectangle drawn on scrap paper. Abstracts which do not conform will not be accepted. Accepted abstracts will be reproduced photographically in the Abstract Volume. Indicate name of expected speaker with an asterisk (*).

Example

Effects of calcium antagonists on the antigen-induced bronchoconstriction
A Tahir*, R Erich and A Wilson
Division of Pulmonary Diseases, Hospital St Pierre, Geneva CH
The purpose of this study was to determine if the

Topics

Please check one option for referred classification of your abstract:

Main Themes

- 1 ☐ Cancer Pain
2 ☐ Non-malignant Pain
3 ☐ Medical Education
4 ☒ Poster Sessions

Scientific Meetings of the Sections

- A ☐ Session 1, Cancer Pain
B ☐ Session 2, Clinical & Scientific Papers on malignant pain
C ☐ Session 3, Non-malignant Pain
D ☐ Session 4, Clinical & Scientific Papers on non-malignant pain
E ☐ Medical Education

Mode of presentation

Please confirm your mode of presentation

- ☐ Slide presentation ☒ Poster ☐ Other (please state)

Mail original copy of your abstract to: Dr Susan Gabris, Edinburgh Symposium,
Napp Laboratories Ltd, Cambridge Science Park, CAMBRIDGE CB4 4GW
Put a piece of cardboard into the envelope to protect your abstract from wrinkle.
Deadline for submission of abstracts is August 12th 1988

All correspondence about this abstract will be sent to:

Title: THE PURDUE FRIEDERICK COMPANY Name: HAUK Initials: HA

Hospice/Institute: THE PURDUE FRIEDERICK COMPANY

Street/No 1100 CONNECTICUT AVENUE

PO Box (if any)

Postal Code 06106 Town NORWALK State CT County USA

Telephone: 2038501213 Telex: 492450 Telefax: 8381576
if available